

**REMARKS**

In this Amendment, claims 1-7 are canceled and claims 8-18 are new. Therefore, after entry of this Amendment, claims 8-18 are all the claims pending in the application.

Initially, Applicants request that the Examiner acknowledge the claim for foreign priority and indicate whether the certified copy of the priority document has been received from the International Bureau.

New claims 8-18 are adequately supported by the specification.

Claim 8 is supported, for example, starting at page 2, second full paragraph through page 4, second paragraph.

Claim 9 is supported, for example, by original claim 2.

Claim 10 is supported, for example, by original claim 3.

Claim 11 is supported, for example, by original claim 5.

Claim 12 is supported, for example, by original claim 1, and page 2, second full paragraph.

Claim 13 is supported, for example, by original claim 7.

Claims 14-15 are supported, for example, by page 4, first paragraph.

Claim 16 is supported by, for example, page 2, lines 25-26.

Claim 17 is supported by, for example, line 26.

Claim 18 is supported by, for example, page 2, lines 26 and 27.

No new matter has been added. Applicants respectfully request entry of the Amendment.

**Response to Objections to the Specification**

At page 2 of the Office Action, the Examiner objects to the disclosure because the word "alcane" is misspelled at page 3.

The required correction has been made. Accordingly, Applicants request that this objection be withdrawn.

**Response to Objections to the Claims**

(A) At page 2 of the Office Action, the Examiner objects to claims 5 and 6 for failing to further limit the subject matter of claims 1 and 3 respectively.

(B) At page 2 of the Office Action, the Examiner objects to claims 2-7. Specifically, the Examiner states that the phrase "characterized by the fact that" is idiosyncratic and unclear, and further, the Examiner suggests that the word "wherein" be used in place thereof.

(C) At page 3 of the Office Action, the Examiner objects to claim 1 because the word "crystallisation" is misspelled.

Claims 1-7 have been canceled in favor of new claims 8-18. Applicants believe that new claims 8-18 adequately address the Examiner's objections, and accordingly, Applicants respectfully request that these objections be withdrawn.

**Response to Claim Rejections Under 35 U.S.C. § 112, Second Paragraph; 35 U.S.C. § 101**

(A) At page 3 of the Office Action, the Examiner rejects claim 1 under 35 U.S.C. § 112, second paragraph, and alternatively under 35 U.S.C. § 101, as allegedly being indefinite and not reciting a proper process claim. Specifically, the Examiner states that claim 1 does not recite the steps involved in practicing the claimed process.

(B) At page 4 of the Office Action, the Examiner rejects claim 6 under 35 U.S.C. 112, second paragraph, because the term "another unit" allegedly renders claim 6 indefinite. The Examiner contends that the disclosure provides no other methods, other than a hydro-cyclone, for the separation.

(C) At page 4 of the Office Action, the Examiner rejects claim 7 under 35 U.S.C. § 112, second paragraph, because the phrase "further purified" allegedly renders claim 7 indefinite. The Examiner contends that since the claimed process is one of simultaneous synthesis and crystallization, further steps of purification are not part of the process.

First, Applicants submit that new claims 8-18 explicitly set forth the steps of the claimed method.

Second, Applicants submit that new claims 8-18 do not use the term "another unit."

Third, Applicants submit that new claims 8-18 do not use the term "further purified." In addition, Applicants submit that the term "purify" as used in new claim 13 is sufficiently understood by one of skill in the art such as to not render claim 13 indefinite.

Accordingly, Applicants assert that new claims 8-18 are not indefinite, and Applicants respectfully request that these rejections be withdrawn.

**Response to Rejections Under 35 U.S.C. § 112, First Paragraph-- Enablement**

At page 4 of the Office Action, the Examiner rejects claims 1-7 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that, while the specification is enabling for certain combinations of amino acids, resulting

dipeptides, and reaction conditions, the specification does not reasonably provide enablement for all X/Y combinations, XY dipeptide products, or reaction conditions.

More specifically, the Examiner contends that: (1) the resulting dipeptide must be sufficiently insoluble in the reaction solvent such that the dipeptide precipitates and crystallizes; (2) only certain hydrophobic AcXOEt and certain hydrophilic YNH<sub>2</sub> can be mixed to form the product AcXYNH<sub>2</sub> that will crystallize simultaneously with formation; and (3) other reaction components such as surfactant, alkane, alcohol, buffer, water, and enzyme have a significant influence on the reaction, and these components must be controlled to minimize side reactions, hydrolysis of the ester, and transesterification with the alcohol.

Claims 1-7 have been canceled in lieu of new claims 8-18. Independent claim 8 recites the dipeptide products described at page 4 of the specification, and in addition, replaces the term “mixture of organic solvents” with the phrase “mixture comprising alkane and alcohol.”

Applicants believe that one of skill in the art in view of the present specification can practice the invention defined by the present claims without undue experimentation. Accordingly, Applicants request withdrawal of this rejection.

#### **Response to Claim Rejections Under 35 USC § 102**

(1) At page 5 of the Office Action, the Examiner rejects claims 1-2, 4 and 6-7 under 35 USC § 102(b) as being anticipated by Serralheiro et al. (1999) in view of Feliciano (2000). Specifically, the Examiner contends that Serralheiro discloses the simultaneous synthesis and precipitation of AcPheLeuNH<sub>2</sub> from AcPheOEt and LeuNH<sub>2</sub> by  $\alpha$ -chymotrypsin in reversed micelles in a Carbosep ultrafiltration ceramic membrane reactor. Further, the Examiner contends

that the process was run in both batch and continuous modes, and that the peptide retained on the membrane was recovered by centrifugation and purified by re-crystallization. Finally, the Examiner contends that Feliciano indicates that the solid dipeptide product that precipitates in this reaction has crystalline properties.

(2) At page 6 of the Office Action, claims 1, 4 and 6-7 are rejected under 35 USC 102(b) as being anticipated by Feliciano (1997) in view of Feliciano (2000). Specifically, the Examiner contends that Feliciano (1997) examines the  $\alpha$ -chymotrypsin catalyzed formation of a number of dipeptides in reversed micelles, and reports that about five of these dipeptides "precipitated" during synthesis from the reaction medium and were collected by centrifugation. The Examiner contends that Feliciano (2000) indicates that the solid dipeptide products that precipitate in this reaction have crystalline properties.

New independent claim 8 recites that the reactor comprises a hydro-cyclone. Since neither Feliciano (1997), Feliciano (2000), or Serralheiro teach such a reactor, the present claims are not anticipated. Accordingly, Applicants request withdrawal of the section 102 rejections.

#### **Response to Claim Rejections Under 35 U.S.C. § 103**

At page 6 of the Office Action, the Examiner rejects claims 1-5 and 7 under 35 USC § 103(a) as being obvious over Serralheiro (1999) and Feliciano (1997) as applied above, and further over US Patent 5,547,858 to Nagano et al. Specifically, the Examiner admits that Serralheiro and Feliciano do not teach the claimed process utilizing a hydro-cyclone. However, the Examiner contends that Nagano teaches using a hydro-cyclone to collect crystals formed simultaneously in a biological synthesis.

The Examiner concludes that a person of ordinary skill in the art at the time the invention was made would have been motivated to use the hydro-cyclone of Nagano in the process of Serralheiro or Feliciano (1997) to collect crystallizing dipeptide product, because both of these biochemical processes produce a crystalline product whose removal is known by simple thermodynamic principles to drive the formation of further product and increase yield.

Applicants request reconsideration and withdrawal of this rejection for the following reasons.

The process of the present invention has properties which have not been explored together in a single, integrated, operation, namely:

- (A) the combination of a synthesis reaction with the simultaneous crystallization of the product formed;
- (B) the use of an ultrafiltration membrane to prevent an enzyme, if used, from exiting the system;
- (C) the coupling of the ultrafiltration module with a hydro-cyclone, enabling the simultaneous existence of two outlet streams from the reactor;
- (D) the removal of secondary products from the system by one of the outlets (the permeate stream from the ultrafiltration module), preventing build-up of secondary products inside the reactor;
- (E) the removal of the product in its crystalline form through the hydrocyclone bottom stream, driving the formation of further product and yield increase.

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Thus, Applicants assert that the successful combination of an ultrafiltration membrane with a hydro-cyclone is not obvious, since clogging of the small membrane pores by growing crystal particles and crystal fragments would have been expected, deteriorating membrane performance and preventing operation of the system. Instead, the obvious option would have been to use the hydro-cyclone after the reaction had been completed.

In view of the above, Applicants request reconsideration and withdrawal of the section 103 rejection.

#### **Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,


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**23373**

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